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PATENT APPLICATION
Attorney's Docket No.: 2007.1000-000

COPY

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Andrew McMichael, Adrian V.S. Hill, Sarah C. Gilbert, Jörg Schneider, Magdalena Plebanski, Tomas Hanke, Geoffrey L. Smith and Tom Blanchard		
Application No.:	09/454,204	Group:	1648
Filed:	December 9, 1999	Examiner:	S. Foley
Confirmation No.:	3485		
For:	Methods and Reagents for Vaccination Which Generate a CD8 T Cell Immune Response		

CERTIFICATE OF MAILING
I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450
on 5-1-03 Karen Sabia
Date Signature
KAREN SABIA
Typed or printed name of person signing certificate

DECLARATION OF DR. JÖRG SCHNEIDER UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Jörg Schneider, of 11 Malford Road, Barton, Oxford, OX3 8BT, United Kingdom, declare and state that:

1. I am Vice President/Director of Research at Oxxon Pharmaccines LTD, the owner of the subject application. I received a diploma in Biology from Julius Maximilians University,

EXHIBIT

Wurzburg, Germany and a Ph.D. in Biology from the University of Mainz, Germany. Upon completion of my studies, I was a post doctoral research fellow in the Molecular Immunology Group, Institute of Molecular Medicine, Nuffield Department of Medicine, John Radcliffe Hospital, Oxford, UK. I have worked extensively in the area of immunology, in particular in the area of the CD8+ T cell response. My C.V. is attached.

2. I am a co-inventor of the invention claimed in the above-reference patent application. I am familiar with the application, including the claims.

3. This Declaration is being filed in order to address the rejection of Claims 46 and 47 as being anticipated by Hodge *et al., Vaccine, 15(6/7): 759-768* (1997). Specifically, this Declaration addresses the Examiner's contention that "[a]lthough Hodge et al. does not specifically teach generating a CD8+ T cell response, Table 2 on page 765 demonstrates T-cell lymphoproliferative responses with the prime-boost regiment, which inherently included CD8+ T cells" (Office Action, page 6).

4. The Doctrine of Inherency has been explained to me. I understand that according to the Doctrine of Inherency, a basis in fact and/or technical reasoning must be provided to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. I understand that inherency may not be established by probabilities or possibilities and that the mere fact that a certain thing may result from a given set of circumstances is not sufficient.

5. Hodge *et al.* immunized mice with a recombinant vaccinia virus containing the human carcinoembryonic antigen (CEA) gene (rV-CEA) followed by a canarypox (ALVAC) expressing the CEA antigen (ALVAC-CEA) and found that CEA-specific T-cell responses were at least four times greater, and far superior to those achieved with three immunizations of ALVAC-CEA. For the reasons provided below, it is unlikely that the T-cell lymphoproliferative responses Hodge *et al.* observed with the rV-CEA prime and ALVAC-CEA boost included CD8+ T cells.

6. In Table 2, Hodge *et al.* show enhancement of CEA specific lymphoproliferative responses of mouse T-cells after immunization with V-Wyeth and rV-CEA, followed by boosting with ALVAC-CEA. However, in the lymphoproliferative assay Hodge *et al.* used to detect a T cell response, "purified human CEA", or whole CEA protein, was the antigen used. Exogenous soluble protein such as the CEA antigen enter the MHC class II presentation pathway, the pathway in which antigens are presented to CD4+ T cells. Exogenous soluble protein cannot readily enter the MHC class I presentation pathway, the pathway in which antigens are presented to CD8+ T cells. The use of soluble CEA protein in the lymphoproliferative assay of Hodge *et al.* indicates that the responding T cells were CD4+ T cells.

7. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true. Moreover, these statements were made with the knowledge that willful, false statements and the like made by me are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any parent issued thereon.

Jörg Schneider

Dr. Jörg Schneider

1st May 2003

Date

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_____

Dr. Jörg Schneider

_____

Date

CURRICULUM VITAE

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ADDRESS	Oxxon Pharmaccines Ltd
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	Littlemore Park
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	Oxford OX44SS
	UK
TELEPHONE	+44 (0)1865 405 135
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DATE OF BIRTH	31 of March 1963, Waiblingen, Germany
NATIONALITY	German

June 1999 – present VP/Director of Research Oxxon Pharmaccines Ltd

As co-inventor of the prime-boost technology I realised that the CD8+ T cell inducing prime-boost technology could be used beyond malaria (see post doc project) in conditions where CD8+ T cells are involved. Involved in initiation and completion of spinout of Oxxon with co-founders, liaised with potential investors to raise seed investment.
Responsibilities 1999-2001: Development and execution of clinical and research plan of Company, report progress to the Board and CEO, managing of contract manufacturing, contract and in-house preclinical testing (toxicity, biodistribution and potency) of DNA vaccines and recombinant viral vectors, co-ordinate preparations of submissions to regulatory authorities in the UK (MCA, GTAC and COREC); co ordinate preparations for phase I studies in the UK using DNA vaccines and recombinant viral vectors; maintain and expand relationships with academic (scientific and medical) collaborators and founders of the Company; support company's patent filings and maintenance; Communicate scientific basis of company to potential investors, licensors and potential partner companies; close involvement in the set-up of the company as Company's Secretary
Responsibilities 2001-present: Due to the growth of the company priority of responsibilities changed to: Develop and communicate scientific strategy/vision for the company, develop and grow internal research capabilities to stay on the leading edge of Oxxon's science base and support of clinical development, manufacturing of clinical trial material, IP and business development strategy, recruited and manage research group of 9 scientists (4 PhDs.)

Sept. 1995 – June 1999 — Post doctoral research fellow in the Molecular Immunology Group (Prof. Adrian Hill), Institute of Molecular Medicine, Nuffield Department of Medicine, John Radcliffe Hospital, Oxford, UK.
Marie Curie Fellow (Training and Mobility of Researchers in the EC, TMR)

Prof. Hill's group was chosen for post doctoral project to work on the development of CD8+ T cell inducing malaria vaccines. Worked mainly on pre-clinical development and cellular immunology of liverstage-specific CD8+ T cell-inducing malaria vaccine. This work lead to the discovery of heterologous prime-boost technology. Supervised research assistant, presentation of work at scientific meetings.

Education

Nov. 1991 - Aug. 1995 — Ph. D. thesis in biology, University of Mainz, Germany,
Title: Recognition of the melanoma antigen MELAN-A/MART-1 by autologous cytotoxic T lymphocytes.
Supervison: P. D. Dr. T. Wölfel
Grade: summa cum laudae
From April 1992 - Aug.1995 Fellow of the: Graduiertenkolleg "Molecular and cellular mechanisms of pathogenesis", Johannes Gutenberg-Universität Mainz, Germany.

Key result of the PhD work was the cloning of the melanoma-associated antigen Melan-A/MART-1 using melanoma-specific CD8+ T cells. This lead to the identification of a HLA-B44-restricted CD8+ T cell epitope. Following this project I realised that new tumour associated antigens will be identified quickly and that ways to induce/use CD8+ T cells will be the major bottleneck in using CD8+ T cells therapeutically. In addition to acquiring solid skills in cellular immunology and molecular biology I developed project management and presentation skills

Sept. 1991 — Diploma in biology (Note: sehr gut), Julius Maximillians University Würzburg, Germany

May 1990 - June 1991 — Diploma thesis in biology, Department for Neurology, University of Würzburg, Germany
Title: Analysis of the cellular immune response against primary brain tumours.

June 1988 - May 1990 — Graduate studies (zoology: cell- and developmental biology, genetics, virology, immunology and organic chemistry, University of Würzburg).
Field project on chimpanzees in a primary tropical rain forest in Taii National Park Cote d'Ivoire, West Africa.

Aug. 1987- May 1988 — University of Texas at Austin,U.S.A., College of Natural Sciences (Fulbright Travel Fellow)

Nov. 1982 - Aug 1987	Undergraduate courses in biology, University of Würzburg (April 1983 - July 1984 civil service in the Department of Neurology at the University Hospital Würzburg
Sept. 1976 - May 1982	Abitur (A-Levels) Aufbaugymnasium, Künzelsau

Publications (Articles and Patents)

Articles:

Hamzel J. McConkey, William H.H. Reece, Vasee S. Moorthy, Daniel Webster, Susie Dunachie, Geoff Butcher, Jenni M. Vuola, Tom J. Blanchard, Philip Gothard, Kate Watkins, Carolyn M. Hannan, Simone Everaere, Karen Brown, Kent E. Kester, James Cummings, Jackie Williams, D. Gray Heppner, Anwar Pathan, Kalle Flanagan, Nirmalan Arulanantham, Mark. T. M. Roberts, Michael Roy, Geoffrey L. Smith, Jorge Schneider, Tim Peto, Robert E. Sinden, Sarah C. Gilbert, Adrian V.S. Hill 2003 Enhanced T-cell immunogenicity in Humans of Plasmid DNA Vaccines Boosted by Recombinant Modified Vaccinia Virus Ankara. *Nature Medicine (In press)*

Tollefson S, Tjoflat T, Schneider J, Harboe M, Wiker H, Hewinson G, Huygen K, Mathiesen I. 2002 Improved cellular and humoral immune responses against Mycobacterium tuberculosis antigens after intramuscular DNA immunisation combined with muscle electroporation. *Vaccine 20(27-28):3370-8*

Gilbert H, Schneider J, Hill AV, Whalen RG. 2002 Role of transfection in the priming of cytotoxic T-cells by DNA-mediated immunization. *Vaccine 20(25-26):3137-47*

Gilbert SC, Schneider J, Hannan CM, Hu JT, Plebanski M, Sinden R, Hill AV. 2002 Enhanced CD8 T cell immunogenicity and protective efficacy in a mouse malaria model using a recombinant adenoviral vaccine in heterologous prime-boost immunisation regimes. *Vaccine 20(7-8):1039-45*

Loke H, Bethell DB, Phuong CX, Dung M, Schneider J, White NJ, Day NP, Farrar J, Hill AV. 2001 Strong HLA class I--restricted T cell responses in dengue hemorrhagic fever: a double-edged sword? *J Infect Dis 184(11):1369-73*

Schneider J, Lacquemanne JA, Gilbert SC, Blanchard TJ, Twigg S, Naitza S, Hannan CM, Aidoo M, Crisanti A, Ronsen KJ, Smith GL, Hill AV, Thomas AW. 2001 A prime-boost immunisation regimen using DNA followed by recombinant modified vaccinia virus Ankara induces strong cellular immune

responses against the *Plasmodium falciparum* TRAP antigen in chimpanzees. *Vaccine 19(32):4595-607*

Hill AV, Reece W, Gothard P, Moorthy V, Roberts M, Flanagan K, Plebanski M, Hannan C, Hu JT, Anderson R, Degano P, Schneider J, Prieur E, Sheu E, Gilbert SC. 2000 DNA-based vaccines for malaria: a heterologous prime-boost immunisation strategy *Dev Biol (Basel) 104:171-9*

Strege MS, Schneider J, Eulitz M, Scholz S, Dornkamm GW, Wolfel T, Reske-Kunz AB. 2000 Consequences of antigen self-presentation by tumor-specific cytotoxic T cells. *Immunobiology 201(3-4):332-46*

Schneider J, Gilbert SC, Hannan CM, Degano P, Prieur E, Sheu EG, Plebanski M, Hill AV. 1999 Induction of CD8+ T cells using heterologous prime-boost immunisation strategies. *Immunol Rev 170:29-38*

Degano P, Schneider J, Hannan HM, Gilbert SC, Hill AVS. 1999 Gene gun intradermal DNA immunization followed by boosting with modified vaccinia virus Ankara: enhanced CD8+ T cell immunogenicity and protective efficacy in the influenza and malaria models. *Vaccine 18(7-8):623-32*

Gilbert SC, Schneider J, Plebanski M, Hannan CM, Blanchard TJ, Smith GL, Hill AVS. 1999 Ty virus-like particles, DNA vaccines and Modified Vaccinia Virus Ankara: comparisons and combinations. *Biol Chem 380:299-305*

Plebanski M, Gilbert SC, Schneider J, Hannan CM, Layton G, Blanchard T, Becker M, Smith G, Butcher G, Sinden RE, Hill AVS 1998 Protection from Plasmodium berghei infection by priming and boosting T cells to a single class I-restricted epitope with recombinant carriers suitable for human use. *Eur J Immunol 28:4345-55*

Schneider J, Gilbert SC, Blanchard TJ, Hanke T, Robson KJ, Hannan CM, Becker M, Sinden R, Smith GL, Hill AVS 1998 Enhanced immunogenicity for CD8+ T cell induction and complete protective efficacy of malaria DNA vaccination by boosting with modified vaccinia virus Ankara. *Nat Med 4:397-402*

Hanke T, Blanchard TJ, Schneider J, Hannan CM, Becker M, Gilbert SC, Hill AV, Smith GL, McMichael A. 1998 Enhancement of MHC class I-restricted peptide-specific T cell induction by a DNA prime/MVA boost vaccination regime. *Vaccine 16:439-445*

Hanke T, Blanchard TJ, Schneider J, Ogg GS, Tan R, Becker M, Gilbert SC, Hill AV, Smith GL, McMichael A. 1998 Immunogenicities of intravenous and intramuscular administrations of modified vaccinia virus Ankara-based multi-CTL epitope vaccine for human immunodeficiency virus type 1 in mice. *J Gen Virol 79:83-90*

Schneider J, Brichard V, Boon T, Meyer zum Buschenfelde KH, Wolfel T. 1998 Overlapping peptides of melanocyte differentiation antigen Melan-A/MART-1 recognized by autologous cytolytic T lymphocytes in association with HLA-B45.1 and HLA-A2.1. *Int J Cancer 75:451-458*

Romero P, Gervois N, Schneider J, Escobar P, Valmori D, Pannetier C, Steinle A, Wolfel T, Lienard D, Brichard V, van Pel A, Jotereau F, Cerottini JC. 1997 Cytolytic T lymphocyte recognition of the immunodominant HLA-A*0201-restricted Melan-A/MART-1 antigenic peptide in melanoma. *J Immunol 159:2366-2374*

Brichard H, Manuiar MJ, Jaggar E, Wolfel T, Schneider J, Karbach J, Seliger B, Huber C, Storkus WS, Lotze MT, Meyer zum Buschenfelde-KH, Knuth A. 1996 Recognition of human renal cell carcinoma and melanoma by HLA-A2-restricted cytotoxic T lymphocytes is mediated by shared peptide epitopes and up-regulated by interferon-gamma. *Scand J Immunol 44:285-292*

Herr W, Schneider J, Lohse AW, Meyer zum Buschenfelde KH, Wolfel T. 1996 Detection and quantification of blood-derived CD8+ T lymphocytes secreting tumor necrosis factor alpha in response to HLA-A2.1-binding melanoma and viral peptide antigens. *J Immunol Methods 191:131-142*

Wolfel T, Hauer M, Schneider J, Serrano M, Wolfel C, Klehmann-Hieb E, De Plaen E, Hankeln T, Meyer zum Buschenfelde K-H, Beach D.1995 A p16INKa-insensitive CDK4 mutant targeted by cytolytic T lymphocytes in a human melanoma. *Science 269: 1281-84*

Coulie PG, Brichard V, Van Pel A, Wolfel T, Schneider J, Traversari C, Mattei S, De Plaen E, Lurquin C, Szikora J-P, Renauld, J-C, Boon, T.1994. A new gene coding for a differentiation antigen recognized by autologous cytolytic T lymphocytes on HLA-A2 melanomas. *J. Exp. Med. 180(1): 35-42*

Wölfel T, Schneider J, Meyer zum Büschenfelde K-H, Rammensee H-G, Rötzschke O, Falk K 1994. Isolation of naturally processed peptides recognized by cytolytic T lymphocytes (CTL) on human melanoma cells in association with HLA-A2.1. *Int. J. Cancer 57(3): 413-418*

Wölfel T, Van Pel A, Brichard V, Schneider J, Seliger B, Meyer zum Büschenfelde K-H, Boon T. 1994. Two Tyrosinase nonapeptides recognized on HLA-A2 melanomas by autologous cytolytic T lymphocytes. *Eur. J. Immunol. 24(3): 759-764*

Jachimczak P, Bogdahn U, Schneider J, Behl C, Meixensberger J, Apfel R., Dorries R., Mehlhorn Grunow K-H, Brysch W. 1993. The effect of transforming growth factor-beta 2-specific phosphorothioate-anti-sense oligodeoxynucleotides in reversing cellular immunosuppression in malignant glioma. *J. Neurosurg. 78(6): 914-921*

Patents

WO 99/05919 Reagents for vaccination which generate a CD8+ T cell immune response (Granted in Europe)

WO 01/21201 Use of replication-deficient adenoviral vector to boost CD8+ T cell immune responses to antigen

WO 02/24224 Vaccination Method